Author’s response to reviews

Title: A population-based cohort study of mortality of intensive care unit patients with liver cirrhosis

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Response to reviewers
To Reviewer 1:
1. Q: How about the history of alcohol-related cirrhosis and hospitalization prior to ICU admission.
   Reply: In this study, history of cirrhosis included alcohol-related cirrhosis. By your comments, we performed the subgroup analysis for investigating the impacts of previous alcohol-related cirrhosis and previous hospitalization on the 30-day mortality of ICU admission. Please see Table 3. The corresponding descriptions were also added in the Results section.
   Thanks for the comments.

2. Q: The authors could consider use Odds Ratio and confidence intervals to present the data in Table.
   Reply: We totally agree with your comments. In fact, we used odds ratios and 95% confidence intervals to present data in Table 2 and Table 3.
   Thanks for the suggestions.

To Reviewer 2:
1. Q: Could the authors discuss the methods since control group was strictly similar to cirrhosis group, that is quite surprising…
   Reply: In fact, we used propensity-score matching combined frequency matching to select very similar case group and control group. This matching method has been used in our previous studies. [Atherosclerosis 2019;282:85-90] [Acupunct Med 2019;37(3):175-183] [BMC Complement Altern
By your comments, we revised the sentence as “To reduce confounding bias, we used a propensity score-matched pair combined with frequency matching procedure to balance the covariates between ICU patients with and without liver cirrhosis”.

Thanks for the comments.

2.
Q: Was the diagnosis of cirrhosis really validated? Could some patients with hepatitis without cirrhosis be included in cirrhotic group?

Reply: In this study, people who had at least two visits of medical care with physician’s primary diagnosis of liver cirrhosis were identified as patients with liver cirrhosis. We also used this definition in our previous studies [BMJ Open 2017;7:e017342] [Atherosclerosis 2017;263:29-35] [Br J Surg 2013;100:1784-1790]. However, among studies based Taiwan’s National Health Insurance Database, there was no validation studies focus on liver cirrhosis. We could not exclude the possibility that some patients with hepatitis without cirrhosis were included in cirrhotic group in this study. By your comments, we added this point as our study limitations in the Discussion section. Thanks for the comments.

3.
Q: In patients hospitalized in ICU, I think that biological parameters can be obtained in registers. So, was there a difference in mortality rates according to Child-Pugh status, or MELD score?

Reply: Because our study is based on the claims data of Taiwan’s National Health Insurance, biological parameters could not be obtained in this database. We have stated in the Discussion that the unavailable information of Child-Pugh score, or MELD score was our study limitations. We are so sorry that in Taiwan’s National Health Insurance Research Database, the results of biochemical measures and physical examinations were not available. Please understand our situations. Thanks for the comments.

4.
Q: Could the authors provide an actuarial survival starting at the day of ICU admission?

Reply: By your comments, we added the analysis regarding actual survival starting at the day of ICU admission. Please see the Table S5. Thanks for the suggestions.

5.
Q: What kind of specific protocol can be applied to improve the management of cirrhotic patients?? Will the result of these series modify the rate of ICU admission in end-stage cirrhotic disease, such as patients with C child's score?

Reply: The results of our investigation in cirrhotic patients admitted to ICU can be integrated to some ICU scoring systems. For example, the APACHE II (Acute Physiology and Chronic Health Evaluation II) score is widely used to estimate ICU mortality but cirrhosis is only one option of chronic organ insufficiency. If we apply cirrhosis and its related clinical indicators, such as ascites or jaundice, to APACHE II scoring system, as independent factors, more accurate mortality may be predicted in patient of different severity. It will provide physicians more information to make clinical decision, such as which medicine or procedure to give. According to our results, the patients with C child’ score, which represent at least moderate to severe encephalopathy, ascites, jaundice and coagulopathy, have
much higher mortality than those with less severity. We should be more vigilant and lower the threshold of ICU admission in patients of end-stage liver disease. It means of the rate of ICU admission will be increased if we modify our clinical practice. Thanks for the comments.